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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,229	REITER ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *141-160 and 196-211* is/are pending in the application.

4a) Of the above claim(s) *150 and 200-211* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *141-149,151-160 and 196-199* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 141-160 and 196-211 are pending in the application.

2. In the prior action, claims 141-160 were pending and rejected.

3. In the Response of August 24, 2007, the Applicant amended claims 141, 150, and 151; and added new claims 196-211.

Amended claim 150, and new claims 200-211 read on non-elected subject matter. These claims are therefore withdrawn from consideration.

4. Claims 141-149, 151-160, and 196-199 are under consideration.

Priority

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. It was noted in the prior action that the Applicant had not complied with the condition for receiving the benefit of an earlier filing date under 35 U.S.C. 120 requiring that the present application correctly include reference prior application 10/396,578, including provision of the relationship between the present application and the prior application. In view of the amendment of the specification, the Applicant's claim for priority now meets the requirements of 35 U.S.C. 120.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. **(New Rejection- Necessitated by Amendment)** Claims 197 and 198 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of these claims depends from cancelled claim 161. It is therefore not clear what invention these claims are describing. For the purposes of this action, the claims are treated as depending from claim 196.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. **(Prior Rejection- Restated as Necessitated by Amendment, and Maintained)** Claims 141 and 144-160 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using antibodies to kill or damage cells using the indicated antibodies where the antibody or fragment thereof is attached to a toxin, does not reasonably provide enablement for methods of killing or damaging cells merely through the exposure of the cells to the antibodies. Claim 150 has been amended such that it no longer reads on the elected invention. The rejection is therefore withdrawn from this claim.

In addition, claim 141 has been amended to require that the antibodies (or binding fragments thereof) not only bind to the indicated complexes, but that they do so in such a manner that they do not bind to the individual components of the complex when exposed to them individually.

In view of the amendment, the rejection is restated as a rejection of claims 141-149, 151-160, and 196-199 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of killing cells comprising the heavy and light chain variable regions of Fab T3F2 as described on page 72 of the application, wherein the antibodies comprises both the antigen-binding region and a functional domain permitting the antibody to kill the target cells, does not reasonably provide enablement for the claimed methods wherein the antibody may be any antibody that meets the functional limitations of claim 141, or a fragment of such an antibody.

This restated rejection includes two basis of rejection. First, the claims are rejected for the reasons indicated in the prior action (i.e. based on the fact that an antibody or fragment thereof comprising only an antigen-binding region is not capable of killing cells). The Applicant traverses the rejection on the basis that the teachings of the application provide teachings that negate the need for the presence of the toxin to kill cells, i.e. through the inclusion of referenced Fc regions. However, it is noted that the claims are drawn to the use of any antibody or fragments thereof that comprises an antigen-binding region. Moreover, while the dependent claims indicate various means for achieving such killing ability, the presence of such dependent claims indicates that the generic claims do not require the presence of such additional functional structures. The only requirement in the rejected claims with respect to the antibody is that the antigen-binding region is present.

The Applicant asserts that the teachings of the application provide enabling support for the claimed inventions. However, it is noted that in each instance where the application teaches that the antibodies may be used to kill cells, the specification teaches that additional elements to

the antigen-binding regions are required. See e.g., page 22 lines 23-27, and page 27 lines 7-20 (teaching the inclusion of certain constant domain sequences to permit targeted cell killing); and page 34 lines 19-27 (teaching the use of a functional moiety such as a toxin). Thus, as indicated by the application, the Applicant's arguments, and the art cited in the Response, more is required than the antigen-binding region in order for the antibodies (or fragments thereof) to kill the targeted cells. Thus, because the teachings of the application and the art indicate that the antigen-binding regions alone is insufficient to kill cells, the rejection of the claims for exceeding the scope for which enabling support has been provided on the previously asserted ground of rejection is maintained.

The second basis of rejection is concerned with the additional claim language of claim 141, which requires that the antibody be capable of binding to the target antigen-presenting molecules (APM)/antigen complex without being capable of binding to either of the two (the APM or the antigen) individually. In support of their arguments in traversal against the previously made obviousness rejection, the Applicant amended the claims to insert the additional functional language, and provided two declarations and other evidence indicating that the process for obtaining such antibodies is " a difficult task," and that those in the art have been trying, and failing, to do so for a long time. See, the DeLisi and Cerundolo Declarations.

The teachings provided by the Applicant in these declarations indicate that there is a great deal of unpredictability and complexity in the task of identifying antibodies that meet the required functional limitations. However, in contrast to these teachings, the application provides no means for overcoming the difficulties of the past other than providing a mere brute force

method of performing multiple levels of screening on large phage libraries of potential antibodies. See e.g., page 71. It is noted that while the Applicant did identify a number of antibodies that purportedly meet the newly added functional limitations, the application teaches that the identification of so many antibodies was "unexpectedly high." Page 71, lines 23-26. It is also noted that the application provides no indication that this method of obtaining an unexpectedly high number of antibodies could be repeated with respect to other target antigens, as the application discloses a method of obtaining antibodies against only one example of an APM/antigen complex. Moreover, in view of the teachings of the two Cerundolo and DeLisi declarations, there is indication that the production of other such antibodies would be unpredictable at best.

With respect to the disclosed antibodies, it is noted that they were indicated above to "purportedly meet the newly added functional limitations." This is because it is not clear that the disclosed antibodies do in fact meet the additional function requirements of not recognizing the APMs or antigens individually (i.e. not as part of the APM/antigen complex). The screening method by which these antibodies were obtained is described on pages 70-72 of the application. However, there does not appear to be any mention in this method for screening antibodies for the inability to recognized the non-complexed APMs or antigens. Thus, it is not clear that the application has in fact provided working examples of the antibodies to be used in the claimed methods. In any case, the application provides little guidance as to what antibodies would bind to other APM/antigen complexes from the complex used in the examples of the application, or as to what portions of the complexes are likely to be targeted by antibodies meeting the functional limitations of the claims. .

It is further noted that the declaration and evidence provided by the Applicant asserting uncertainty in the art were provided in response to a rejection asserting a that the art teaches how to make antibodies targeting APM/antigen complexes. It is noted that the art cited indicates that the antibodies may be identified through the use of phage display (See e.g., Reiter et al., PNAS 94:4631-37, at 4631- stating that the antibody targeting the murine APM complexed with an antigen was identified through such a method). Thus, the Applicant has asserted unpredictability even with respect to the use of a method such as the one disclosed by the Applicant to identify the antibodies of interest. Thus, the evidence and the arguments by the Applicant appear to indicate that the "unexpected" results of the present application were outside the norm, and that the fact that the Applicant's succeeded in identifying antibodies directed against one APM/antigen complex is not necessarily enabling for the making and use of antibodies directed against any such complex.

In view of the uncertainty and complexity in the art, the limited guidance in the application, and the limited (if any) working examples present in the application, the claims are rejected as lacking adequate support to enable the scope of the presently claimed inventions.

10. **(Prior Rejection- Maintained)** Claim 150 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement with respect to a genus of methods comprising the use of an antibody or fragment thereof that binds to a human antigen-presenting molecule/antigen complex wherein the fragment comprises the sequence of SEQ ID NO: 23. Claim 150 has been amended such that it no longer reads on the elected invention. New claim 199 has been added to the application in the place of claim 150. This claim reads on the

method of claim 141 wherein the antibody comprises the sequences of SEQ ID NOs: 20-25. It is noted that these sequences are identified in the application as corresponding to the CDRs in the T3F2 Fab disclosed in Table 3 (page 72) of the application.

However, as was indicated in the prior action, the teachings of the art indicate that the amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity that is characteristic of the parent immunoglobulin, and that those in the art would have expected that all of the heavy and light chain CDRs **in their proper order** and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having a specified antigen-binding function. The present claim does not require any particular order for the indicated CDRs, or indicate that the indicated CDRs are to be found on one variable domain or the other. Thus, the claim reads of embodiments wherein the CDRs may be in any order, and wherein each CDR may be present in either the heavy or light variable chain. For the reasons indicated in the prior action, the rejection is therefore maintained against this claim.

11. **(New Rejection- Necessitated by Amendment)** Claims 14-149, 151-160, and 196-198 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. hese claims have been amended to read on methods of using any of a genus of antibodies that are described as capable of binding to a complex "composed of a human antigen-presenting

molecule and an antigen," and wherein the antibody "does not bind the antigen-presenting molecule in an absence of the antigen... and the antibody does not bind the antigen derived from the pathogen in an absence of the human antigen-present molecule." The claims are rejected as exceeding the scope for which adequate descriptive support has been provided.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

However, the presence of multiple species with in a claimed genus does not necessarily demonstrate possession of the genus. See, In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the

prosecution of a patent application."); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support).

The present claims are rejected because the application has not provided adequate written description support for the claimed genus of antibodies being used in the claimed method. With respect to this genus, it is noted that the application discloses the CDR sequences of 14 different antibodies according to the present claims. However, each of these antibodies is directed to a single antigen-presenting molecule (APM)/antigen complex- the complex disclosed on (e.g.) page 70 as comprising a recombinant human HLA-A2 MHC, beta2-microglobulin, and a specific HTLV-1 Tax peptide. No antibodies binding to any other such complexes have been disclosed. Thus, relative to the scope of the genus claimed, the number and characteristics of the disclosed antibodies is extremely narrow. Moreover, it is not clear from the teachings of the application that the identified antibodies meet the newly added functional limitations of the claims. There does not appear to be any screening of the identified antibodies for the inability to bind to the APMs or antigens other than as part of the APM/antigen complex. See e.g., the description of the screening methods on pages 70-72 of the application. Thus, it is not clear that the disclosed species are in fact representatives of the genus of antibodies described by the claims.

As was indicated in the prior action, the art recognized that the binding characteristics of antibodies are extremely sequence specific. At present, the art provides no means by which to predict what antibodies would bind to any given antigen based solely on a disclosure of the antigen. It is noted that the Office generally accepts that disclosure of the target antigen is sufficient descriptive support for a genus of antibodies binding such. See e.g., MPEP 2163 II.A.3.(a); and *Noelle v. Lederman*, 69 U.S.P.Q.2d 1508, 1513-14 (CAFC 2004). However, the

facts of the present case vary from those indicated in the MPEP and in *Noelle* in two respects. First, the present claims are not merely directed to an antibody that binds to the indicated antigen. Rather, the antibodies of the present claims require additional functional features (i.e. they bind to a complex of antigens; but do not bind to any of the antigens when present outside of the complex).

Second, in the present case, the Applicant has presented evidence that the mere provision of the complex is not alone sufficient to obtain the antibodies described in the present claims. See e.g., the declarations of Vincenzo Cerundolo and Charles DeLisi (both filed on July 24, 2007). In both of these declarations, the Applicant states that the processes for obtaining the antibodies according to the present claims "is a difficult task" and note numerous attempts by others to do so that have failed.

Thus, in the present case, the claims are directed to a subgenus of antibodies described as having functional characteristics in addition to the mere binding of a target antigen, wherein the teachings in the art and provided by the Applicant indicate that there is significant uncertainty in the operation (and identity) of other antibodies than those few provided. Because the disclosed species are not representative of the full scope of the genus claimed, and in view of the complexity in the art regarding obtaining other antibodies according to the claimed, the claims are rejected as exceeding the scope for which adequate descriptive support has been provided.

It is further noted that the application discloses a method for the production of the antibodies used in the claimed methods. However, the Court of Appeals for the Federal Circuit has indicated that the provision of such a method does not provide adequate descriptive support for compounds that me be identified through its use. See e.g., *University of Rochester v. G.D.*

Searle & Co., 69 U.S.P.Q.2d 1886, at 1895 (2004). For the reasons indicated above, the present claims are rejected as exceeding the scope for which adequate descriptive support has been provided.

Claim Rejections - 35 USC § 103

12. **(Prior Rejections- Withdrawn)** Claims 141-149, 151-155, 158, and 159 were rejected under 35 U.S.C. 103(a) as being unpatentable over Reiter (PNAS 94: 4631-36) , further in view of the teachings of Andersen et al., (WO 97/02342). Claims 141-149 and 151-159 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reiter and Andersen as applied above, further in view of the teachings of Matsushita et al. (U.S. 5,591,829- of record in the September 2005 IDS). Claims 141-149 and 151-160 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reiter and Andersen as applied above, further in view of the teachings of Saito et al. (J Virol 75: 1065-71- of record in the September 2005 IDS). In view of the Applicant's amendment of the claims, the arguments and declarations submitted by Applicant, the rejections are withdrawn.

13. **(Prior Rejection- Withdrawn)** Claims 141-160 were rejected under 35 U.S.C. 103(a) as being obvious over Reiter, Andersen, and Saito as applied to claims 141-149 and 151-160 above, further in view of Hoogenboom et al. (U.S. 2003/0223994- of record in the September 2005 IDS). In view of the Declaration of Yoram Reiter, removing the Hoogenboom reference as applicable prior art, this rejection is withdrawn.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. **(Prior Rejection- Maintained)** Claims 141-160 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48-50 of copending Application No. 11/203,137, or the copending claims in view of the teachings of Reiter and Andersen in view of any of Hoogenboom, Matsushita, or Saito as applied above. Applicant presented no arguments in traversal of the rejection. It is noted that, while the present claims have been amended, the copending claims also render obvious methods of using a specific antibody, which was identified with a method such as the one used in the present application, and which would therefore be expected to have the same or similar binding characteristics. The rejection is therefore maintained.

16. **(Prior Rejection- Maintained)** Claims 141-160 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8, 11, of copending Application No. 11/629194, or the copending claims in view of the teachings of

Reiter and Andersen and Hoogenboom as described above. It is noted that, while the present claims have been amended, the copending claims also render obvious methods of using a specific antibody, which was identified with a method such as the one used in the present application, and which would therefore be expected to have the same or similar binding characteristics. The rejection is therefore maintained.

Conclusion

17. No claims are allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Z. Lucas/
Patent Examiner, AU 1648